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Retinoblastoma

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A. Incidence of Retinoblastoma

Retinoblastoma is the most frequently occurring neoplasm of the eye in childhood, occurring in about 1 in 14,000–18,000 live births.[1, 2] Thus, an estimated 300 children develop retinoblastoma each year in the United States and about 8000 cases will occur worldwide.[3] Most cases of retinoblastoma will occur in children in developing countries. However, the incidence of retinoblastoma may not be not distributed equally throughout the world. Although retinoblastoma appears to occur more frequently in some areas of Africa and India, and among children of Native American descent in the North American continent [3, 4] it is difficult to prove owing to the lack of population-based studies.

Recently, some well-designed studies have shown an increased incidence of retinoblastoma in some areas of Brazil and Mexico,[5, 6] but whether these geographical variations are due to ethnic or socioeconomic factors is unknown.

Retinoblastoma presents in 2 distinct clinical forms. The first is a hereditary bilateral or multifocal form (40% cases), characterized by the presence of germline mutations of the *RB1* gene. Hereditary retinoblastoma may be inherited from an affected survivor (25% cases) or may be the result of a new germline mutation (75% cases). The second is a nonhereditary form (60% cases of which 90% cases are unilateral or unifocal). However, since approximately 10% germline cases involve unilateral disease, without genetic screening, it is not possible to determine which unilateral cases are capable of being transmitted to the next generation in the absence of a supportive family history.

A. 1 *Clinical Manifestations*

Retinoblastoma is a tumor of the retina that affects young children and the age at presentation correlates with laterality and the lateness of diagnosis. Patients with bilateral retinoblastoma tend to present at a younger age (usually before 1 year of age) than do children with unilateral disease, who often present in the second or third year of life. Half of the cases of retinoblastoma patients diagnosed during the first year of life have bilateral disease, as opposed to less than 10% of those diagnosed after the first year of life. It is uncommon for retinoblastoma to be diagnosed during the first month of life, except in familial cases where early examination is recommended. However, regardless of the family history, more than 90% neonatal cases either have bilateral disease at presentation or will eventually develop asynchronous bilateral retinoblastoma.

The presenting features of retinoblastoma vary depending on the geographic location of an affected child.

In developing countries, extraocular extension is more common, so patients often present with proptosis and an orbital mass, possibly with preauricular adenopathy (**A. Figure 1**).[7] In such settings, it is not uncommon to find severely affected children with extensive extraocular disease presenting with malnutrition and irritability due to glaucoma, increased intracranial pressure, or fever of unknown origin.[8]

A. Figure 1
Proptosis and leukocoria in a child with retinoblastoma.

In developed countries, the most common presenting sign is leukocoria, sometimes initially noticed in a flash photograph (**A. Figure 2**).[9] Even though leukocoria is an unambiguous sign with a small range of differential diagnoses, it is often overlooked by pediatricians. Strabismus is the second most common presenting sign and is usually associated with macular involvement.

A. Figure 2
A child with retinoblastoma presenting with leukocoria.

Strabismus is a nonspecific sign that is often present in normal children, so it is also often overlooked as a sign of retinoblastoma. Very advanced intraocular tumors may become painful as a result of secondary glaucoma, and older children may report poor vision. The differential diagnosis should include other childhood diseases that can present with leukocoria, such as persistent hyperplastic primary vitreous (PHPV), retrolental fibrodysplasia, Coats disease, congenital cataract, toxocariasis, and toxoplasmosis. Patients may also present with pain and redness in the eye, and orbital swelling similar to that seen in orbital cellulitis, although this presentation does not necessarily indicate extraocular extension.[9]

In familial cases, the diagnosis is usually made through screening, although almost 50% of familial cases are diagnosed later in life, when patients present with the typical signs of retinoblastoma. This underscores the importance of genetic counseling. In developing countries, familial retinoblastoma is diagnosed by screening in fewer than one-fourth of all cases.[10] Since tumors can develop in children up to 28 months of age, children

with a family history of retinoblastoma should receive a thorough ophthalmological examination under anesthesia shortly after birth and periodically thereafter.[11]

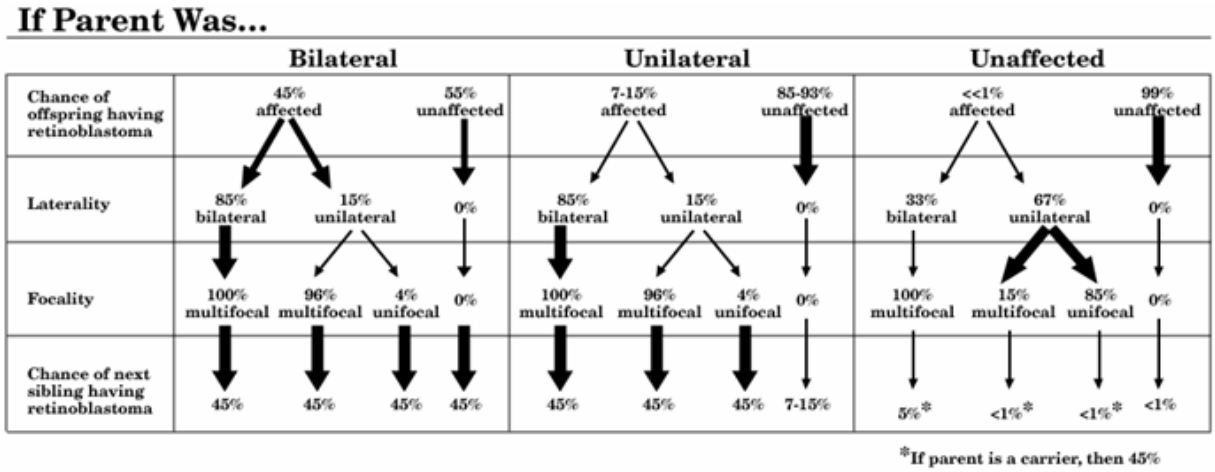
Although most patients with bilateral retinoblastoma carry a germline mutation of the *RB1* gene, only a small proportion (5%–6%) carry a deletion involving the 13q14 locus, which is large enough to be detected by karyotype analysis. Patients with the 13q-syndrome have typical dysmorphic facial features, subtle skeletal abnormalities, and various degrees of mental retardation and motor impairment.[12] Dysmorphic features that are consistently found include thick anteverted ear lobes, a high and broad forehead, a prominent philtrum, and a short nose. Some patients also have overlapping fingers and toes, microcephaly, and delayed skeletal maturation. The severity of such deficits correlates with the size of the deletion; psychomotor development may be normal in cases where the deletion is restricted to the 13q14 band.

More Oncopedia resources on presenting signs of retinoblastoma:

- Nystagmus as a Presenting Sign of Retinoblastoma
- Strabismus as a Presenting Sign of Retinoblastoma
- Presenting Signs of Early Retinoblastoma in an Infant
- Retinoblastoma Presenting as Preseptal Cellulitis

A. Figure 3
A patient with 13q14 syndrome

A. Table 1
Tips for Genetic Counseling[+]



[+]DH Abramson (with permission)

A. 2 *Genetics of Retinoblastoma*

In 1971, retinoblastoma was the first cancer to be described as a genetic disease. At that time, Knudson proposed the "two-hit hypothesis", in which two mutational events in a developing retinal cell lead to the development of retinoblastoma. Later, other investigators extended this notion to suggest that the two events could be mutations of both alleles of the *RB1* gene. The *RB1*, is located within the chromosome 13q14; its product, pRb, is a key substrate for G1 cyclin-cdk complexes, which phosphorylate target gene products required for the transition of the cell through the G1 phase of the cell cycle. pRb stands is considered as the major gatekeeper to control this critical point in growth regulation and its inactivation removes the constraint on cell cycle control, with the consequence of deregulated cell proliferation.

The molecular diagnosis of retinoblastoma is limited because the *RB1* is a large gene, and all axons may harbor mutations. Additionally, no mutational hot-spots were identified but paternal alleles are preferentially involved in new germ-line mutations. In both hereditary and non-hereditary retinoblastoma, the second tumorigenic event is usually chromosomal in nature, often as a result of mitotic recombination errors. This second hit occurs at a much higher frequency than the first hit. It is probable that this phenomenon and the fact that they are more sensitive to environmental factors such as ionizing irradiation may contribute to the increased risk of irradiation-induced malignancies in survivors of retinoblastoma.

After the *second hit* has taken place, retinoblastoma cells rapidly accumulate additional genetic damage, and tumors develop. Even though retinoblastoma is one of the tumors in which these molecular pathways have been identified in greater detail, its pathogenesis remains incompletely understood. Murine retinoblastoma models have played a significant role in the understanding of these mechanisms. Interestingly, when hemizygous mutations of the retinoblastoma gene are induced, these animals do not develop retinoblastoma. Instead, they develop midbrain tumors and "knock-out" mice die at gestational day 14 due to hematopoietic and neuronal defects. Other members of the retinoblastoma gene family, such as *p107*, play a role in the abrogation of tumor formation in mice (through a compensatory up-regulation, for example).

However, this phenomenon is not seen in human retinoblastoma when *RB1* is inactivated.

Recently, the first knockout mouse models of retinoblastoma were generated by conditionally deleting *Rb* in retinal progenitor cells of *p107*-deficient mice. The *p53* pathway plays a key role in the retinoblastoma tumorigenesis, however, it is not mutated in human retinoblastoma. When it is simultaneously inactivated in *RB;p107*-deficient retinal progenitor cells, a more aggressive form of retinoblastoma, similar to the human disease, is observed. Therefore, although the biallelic loss of the *RB1* gene is a rate-limiting step for the development of retinoblastoma, additional mutations or gene amplifications are required. The inactivation of both the *p16Ink4a-CycD/Cdk4-pRb* and *Arf-MDM2/MDM4-p53* pathways is believed to be important in retinoblastoma tumorigenesis. It is especially important the role of *p14ARF* in the *p53* tumor surveillance pathway. When pRb activity is lost, the transcription factor E2F activates transcription of *p14ARF*; *p14ARF* then inactivates *MDM2*, leading to *p53*-mediated apoptosis and exit from the cell cycle. Therefore, loss of *RB1* in the developing human retina (or loss of *Rb* and *p107* in the mouse retina) should cause de-repression of *Arf* and activation of the tumor surveillance mechanism. In human retinoblastoma wild-type *p53* is expressed, so, it was assumed that the p53 pathway was intact. Therefore, other genes in the pathway (such as *p14ARF, MDM2* and *MDM4*) were not usually considered important.

A recent study has shown that inactivation of the Rb pathway in the developing mouse or human retina leads to ectopic proliferation and activation of the Arf-MDM2/MDM4-p53 tumor surveillance pathway. The ectopic proliferation caused by the loss of the Rb pathway is balanced by *p53* mediated apoptosis. Therefore, a critical event in retinoblastoma tumorigenesis appear to be *MDM4/MDM2* amplification leading to inactivation of the *p53* pathway. These findings are important for identifying newer molecular targets. In 2013, a special subset of retinoblastoma patients lacking identifiable mutations of the Rb1 gene was reported from multiple institutions. This uncommon feature is present in about 2% of the cases and it has been associated to MYCN amplification, early age and distinct Histopathological features, however its prognostic implications remain unknown.[13]

A.3 *Differential Diagnosis*

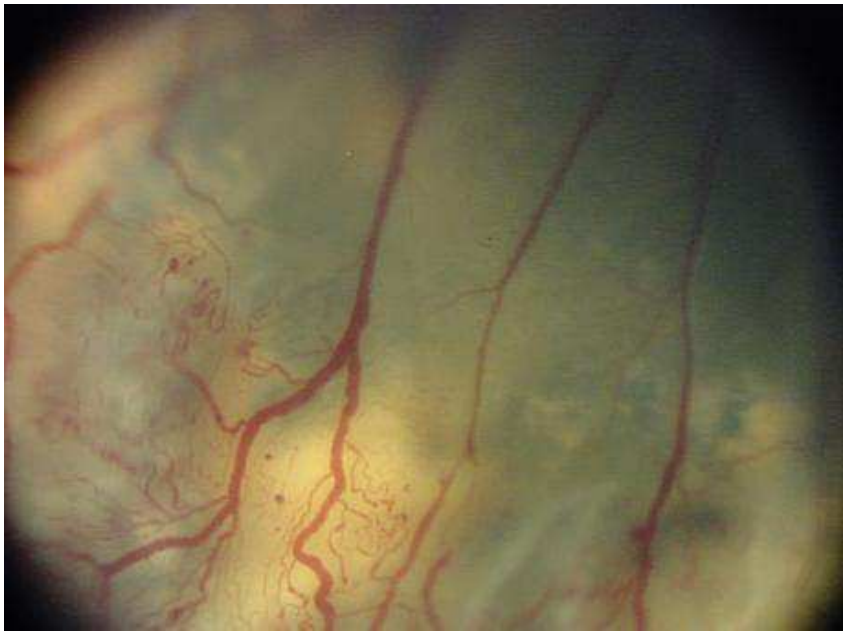
When Retinoblastoma Presents as a Mass

- Medulloepithelioma
- Astrocytic hamartoma
- *Toxocara canis*-induced granuloma
- Infected emboli caused by subacute bacterial endocarditis or toxoplasmosis
- Other types of severe uveitis

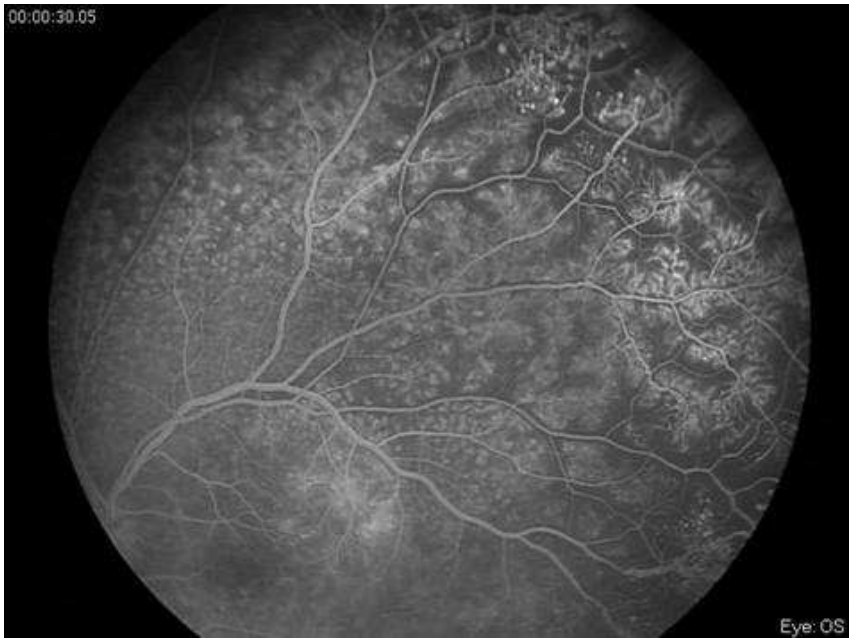
When Retinoblastoma Presents as a Retinal Detachment

- Coats disease
- Retrolental fibroplasia
- PHPV

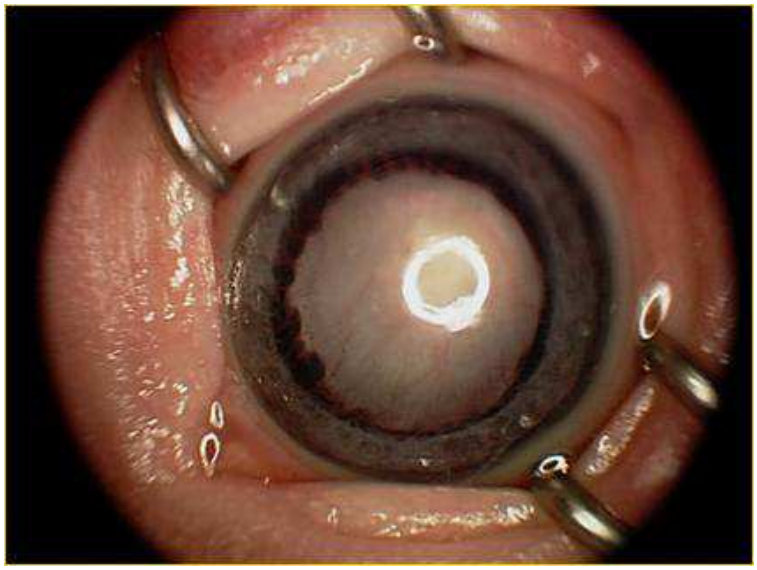
A. Figure 4
Coats disease: Note the massive retinal detachment and telangiectatic vessels.



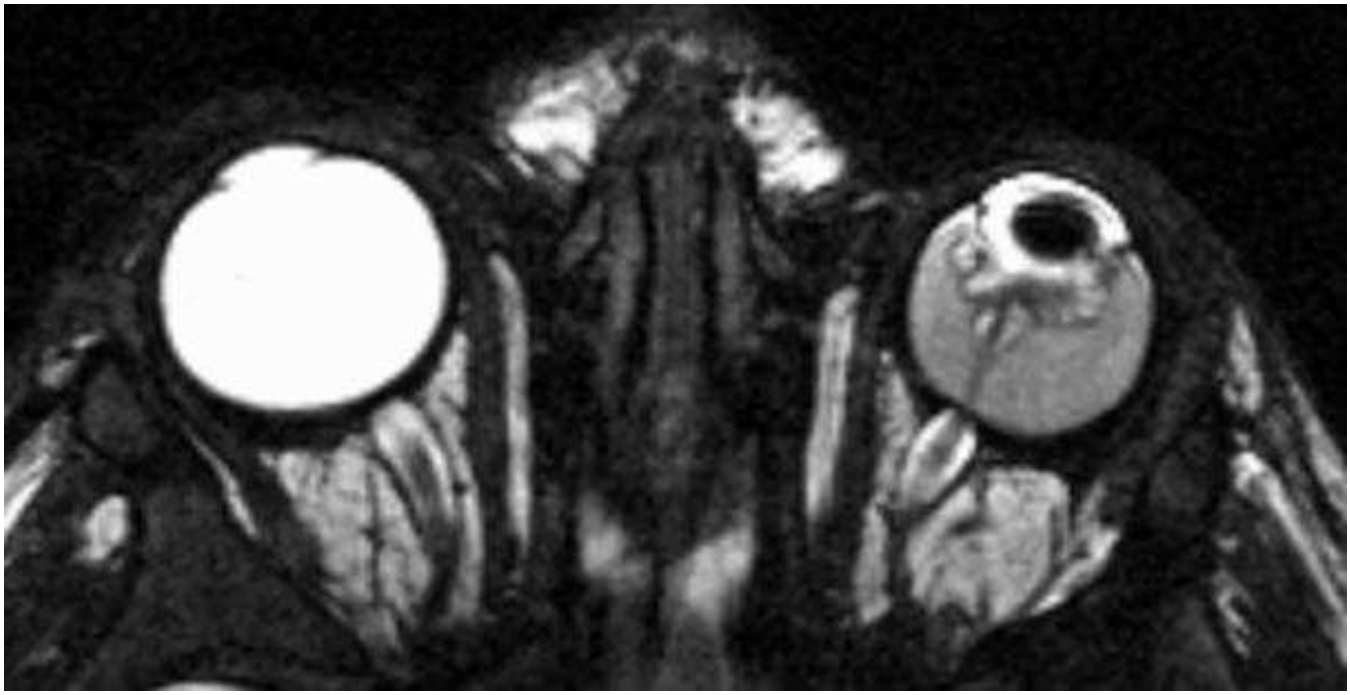
A. Figure 5
Coats disease: Fluorescein angiogram showing telangiectatic vessels.



A. Figure 6
Persistent hyperplastic primary vitreous. Note the elongated ciliary processes



A. Figure 7
MR image showing left microphthalmia, disruption of the anterior segment, and persistence of fetal vasculature—findings consistent with PHPV.



A. Figure 8
Medulloepithelioma showing as an amelanotic mass arising from the ciliary body.

A. Figure 9
MRI image showing a mass with cystic changes, supporting a diagnosis of medulloepithelioma.

More Oncopedia resources on medulloepithelioma and early retinoblastoma:

- Medulloepithelioma of the optic nerve in a 1-year-old child
- Presenting Signs of Early Retinoblastoma in an Infant

A. References

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B. Status of Retinoblastoma in Developing Countries

B.1 *Is Retinoblastoma more Frequent in Developing Countries?*

There is some evidence that retinoblastoma is more frequent in certain populations, for example, in Alaskan natives.[1] In addition, its prevalence is higher in some areas of South America, such as tropical Brazil.[2] Accurate estimation of the incidence of this disease in specific regions is a priority in order to develop strategies for disease control. In an attempt to elucidate the reasons for the increased prevalence of retinoblastoma in specific populations, Orjuela et al. studied sequences of the human papilloma virus (HPV) in enucleation specimens of patients with retinoblastoma in Mexico.[14] Since HPV infection usually affects young women of childbearing age and has a geographic distribution similar to that of retinoblastoma, these researchers suggested that there may be an association between these 2 conditions.

However, a direct effect of the HPV has a direct effect on the development of retinoblastoma is yet to be proven. More recent studies failed to reveal any association between HPV and retinoblastoma.[4,5] Orjuela et al. found that low intake of fruits and vegetables during pregnancy correlated with a higher risk of the baby developing sporadic retinoblastoma in Mexico.[6] Recently, Mexican investigators showed that retinoblastoma is more frequent in the Chiapas region,[5] others described retinoblastoma as the second-most common malignancy in Malawi.[7]

B.2 *Do Media Campaigns for Early Diagnosis Work in Developing Countries?*

Contributor: Dr. Ligia Fu

A campaign for early diagnosis of retinoblastoma was implemented in Honduras, one of the poorest countries in Latin America, where 60% of the population younger than 60 years, a low literacy rate, and socioeconomic problems that include infectious diseases and malnutrition.[15] Even though the care of children with cancer is not a priority among public health offices in Honduras, the medical team at the Unidad de Hemato-Oncologia Pediatrica of the Hospital Escuela,the main tertiary care center in Honduras,developed a comprehensive program, including an early diagnosis campaign, for families with children with retinoblastoma.

The current estimated survival rate of children with retinoblastoma is greater than 90% in developed countries; however, an evaluation conducted in Honduras in 2000, showed that only 15% of children referred to the above center survived. Since many patients presented with advanced disease at the time of diagnosis, we hypothesized that early diagnosis could improve the mortality rate. We therefore designed a program to educate the Honduran population about the link between leukocoria and retinoblastoma. In 2003, we prepared a flyer that included a picture of a child with leukocoria and recommendations for parents to seek medical attention if they suspected that their children could have leukocoria.

B.3 *Is There a Reason for Screening the General population in Developing Countries?*

For many years, children with a family history of retinoblastoma have been screened by examination of the dilated pupil under anesthesia, so, the disease's natural history is well known. Retinoblastoma occurs in individuals within a narrow age interval, which constitutes a well-defined target population

for screening. In addition, children in this age group routinely visit their pediatricians much more than children in any other age group. However, the main aim of screening programs is to reduce the mortality associated with the neoplasm, and these programs, though effective, are not the only way of reducing mortality. Other smaller scale measures may also have an impact on mortality. The mortality rates of patients with retinoblastoma are high in developing countries, mainly because of delayed diagnosis and poor compliance by the affected families.[9,10]

Early diagnosis could improve the chance of providing a cure for these children. Instead of launching costly screening programs that involve the general population, wherein only 1 in 14,000–17,000 cases would be detected, an important initial step could be the effective screening of all affected family members so that all familial cases can be identified while the disease is still intraocular.[9] Reducing the number of cases where treatment is discontinued could also dramatically improve the outcome, especially in children for whom cure is a possibility.[10,11] Measures to reduce both discontinuation of treatment and late detection of familial cases would probably be the most cost-effective initial steps that can be adopted in many developing countries where a treatment program is not well established. Improvements in diagnostic procedures and treatments may also improve the cure rates. Therefore, costly screening programs are difficult to justify in countries with more prevalent health problems, such as poor hygiene, deficient sanitation, lack of universal vaccination, and malaria or other endemic diseases associated with even higher mortality. Economic development and improved accessibility to high-quality medical care are the only sustainable measures that could reduce retinoblastoma-related mortality in developing countries.[9,12]

B.4 *Why is Retinoblastoma Diagnosed Late in Developing Countries?*

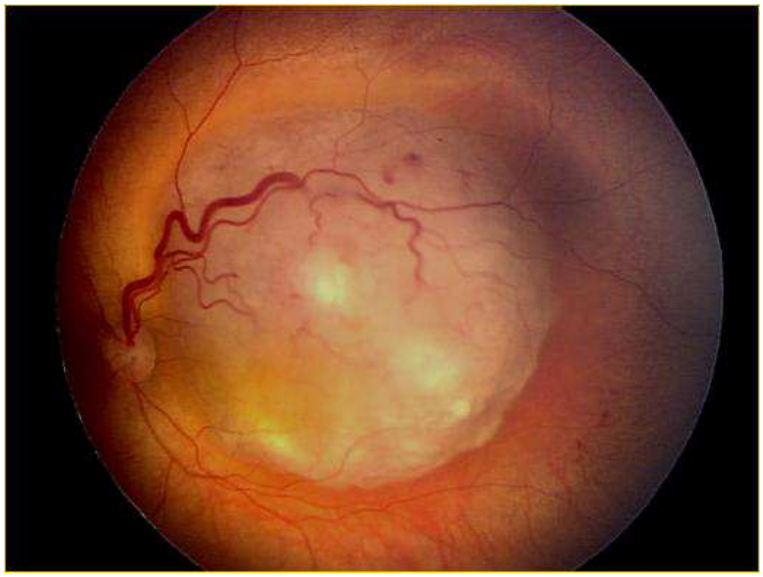
The successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. The extent of disease progression usually correlates with the extent of delay in diagnosis.[13] In developing countries, late referrals are strongly associated with orbital and metastatic disease.

B.5 *Approaches to Diagnosing Intraocular Retinoblastoma*

The diagnosis of intraocular retinoblastoma is usually established by an experienced ophthalmologist, without pathologic confirmation. The retina should be examined under anesthesia, with maximal pupil dilation and scleral indentation. First, the iris and anterior chamber are carefully examined, and the intraocular pressure is measured. Retinoblastoma usually presents as a mass projecting into the vitreous, although the presence of retinal detachment or vitreous hemorrhage may hinder its visualization. Endophytic tumors are those that grow inward into the vitreous cavity. Endophytic retinoblastoma may show seeding in the vitreous cavity because of their friable nature (**B. Figure 1**). Exophytic retinoblastoma grows into the subretinal space, thus causing progressive retinal detachment and subretinal seeding (**B. Figure 2**). Exophytic tumors often show characteristic features of Coats disease. Less frequently, retinoblastoma may exhibit an infiltrative pattern, without an obvious mass (**B. Figure 3**). This infiltrative pattern is more common among older children.

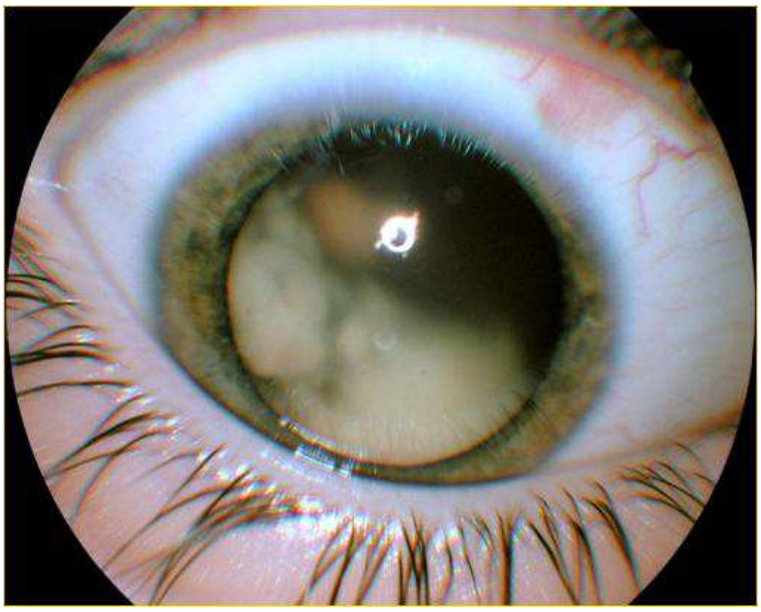
The number, location, and size of tumors; the presence of retinal detachment and subretinal fluid; and the presence of vitreous and subretinal seeding should be documented in detail.

B. Figure 1
Exophytic retinoblastoma. Note the enlarged vessels, areas of calcification, luteal pigmentation denoting the macular origin of the tumor, and small retinal detachment surrounding the tumor.



B. Figure 2
Endophytic retinoblastoma with massive vitreous seeding.

B. Figure 3



More Oncopedia resources about Retinoblastoma in Developing Countries:

- Retinoblastoma orbital relapse in a patient from Sierra Leone
- Orbital relapse after intraocular retinoblastoma
- Ocular fundoscopy in a retinoblastoma patient

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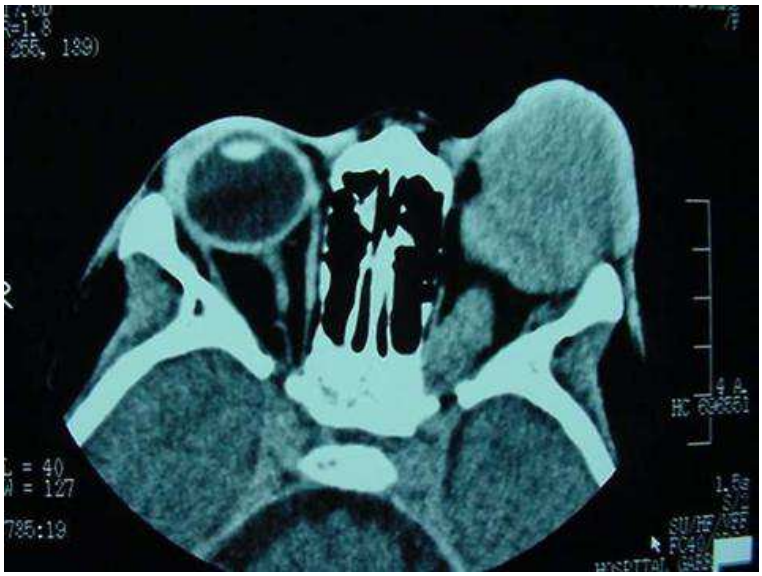
C. Diagnostic Evaluation of Extraocular Extension

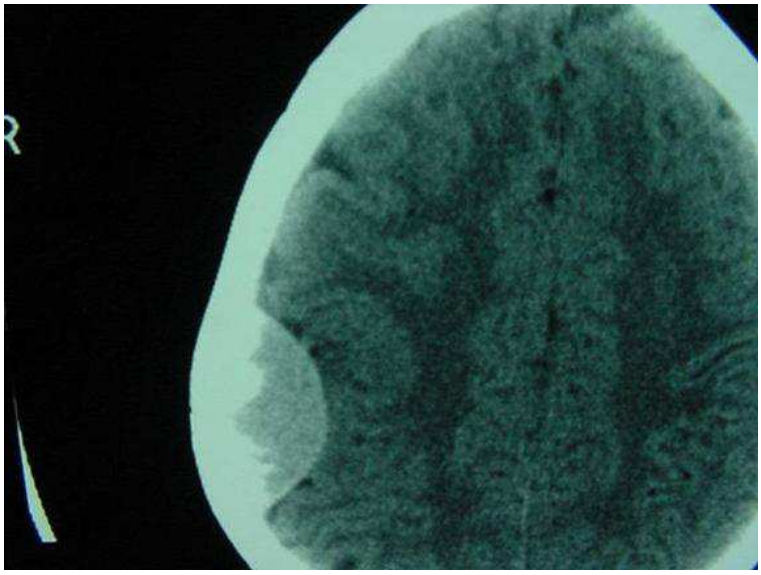
C. 1 *Imaging Studies*

Imaging techniques that aid in the diagnosis of retinoblastoma with extraocular extension include two-dimensional ultrasonography, CT, and MRI. These techniques are particularly important for evaluating extraocular extension and differentiating retinoblastoma from other causes of leukocoria. CT is very useful for detecting calcification, and MRI helps in the differential diagnosis of extraocular extension of retinoblastoma, Coats disease, other inflammatory conditions, and persistent hyperplastic primary vitreous. MRI of the head and orbit should be performed to evaluate the possibility of extraocular extension. MRI is preferred over CT so as to avoid exposing of patients with germline mutations to radiation.[1]

C. Figure 1
Retinoblastoma with massive extension into the orbital and optic nerves (CT scan)

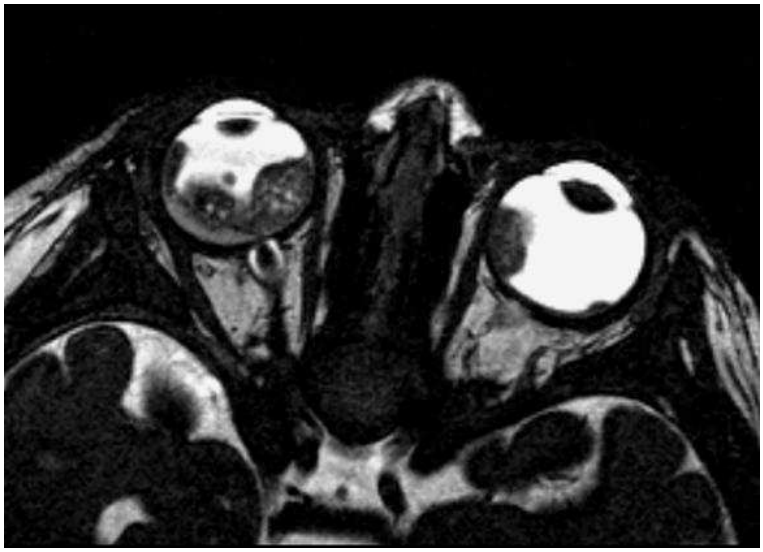


C. Figure 2
Retinoblastoma with metastasis into the skull (CTscan).



C. Figure 3
Retinoblastoma with mandibular metastasis (CT scan)

C. Figure 4
Bilateral retinoblastoma (MR image)



C. 2 *Ancillary Studies*

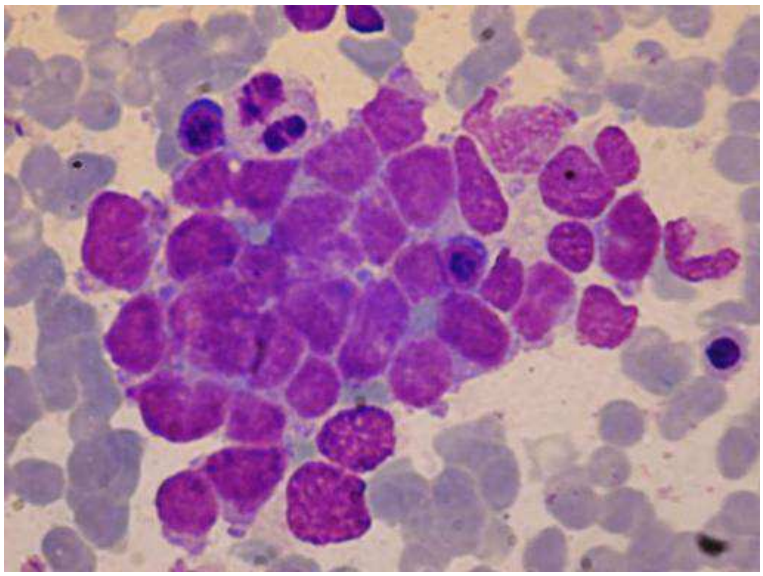
The possibility of metastatic disease should be considered in patients with features that could be high-risk factors for extraocular extension of retinoblastoma.[2] In industrialized countries, metastatic disease occurs in very few patients and usually presents with distinct intraocular histological features, such as extensive choroidal and scleral invasion, involvement of the iris-ciliary body, and optic nerve beyond the lamina cribrosa. In such cases, additional staging procedures, including analysis of bone marrow aspirate, biopsy specimens, and CSF, are warranted.[2] Bone scintigraphy is recommended only for patients with confirmed metastatic disease or bone pain. In asymptomatic patients, its use is controversial, even if pathological risk factors have been detected. Analysis of bone marrow aspirate and biopsy specimens is recommended only for children at high risk, especially in cases of massive extraocular extension.[3] Aspiration from multiple sites and subsequent immunocytological analysis may increase the effectiveness of these procedures. Retinoblastoma cells tend to aggregate into rosettes or clumps (**C. Figure 5**) but may occasionally show diffuse infiltration into the bone marrow, as in the case of leukemia. Further, circulating blasts have been found in patients with advanced disease.[4] A recent study from India suggested that children with stages 0 and I (IRSS) do not need lumbar puncture and bone marrow evaluation for staging. Those with overt extraocular disease obviously need to have the CSF and the BM assessed and those with stage II (tumor at the resection margin of the optic nerve or trans-scleral invasion) may also benefit from it but the population studied was relatively small.[4]

In the view of these controversial data, the authors suggest that bone marrow evaluation and lumbar puncture should not be done in all patients with retinoblastoma. Patients who need to undergo these procedures include:

a) Overt extraocular disease (stages III and IV)
b) Initially enucleated patients with tumor at the resection margin of the optic nerve or beyond the sclera
c) All cases in whom pre-enucleation chemotherapy is done because buphthalmia or glaucoma.

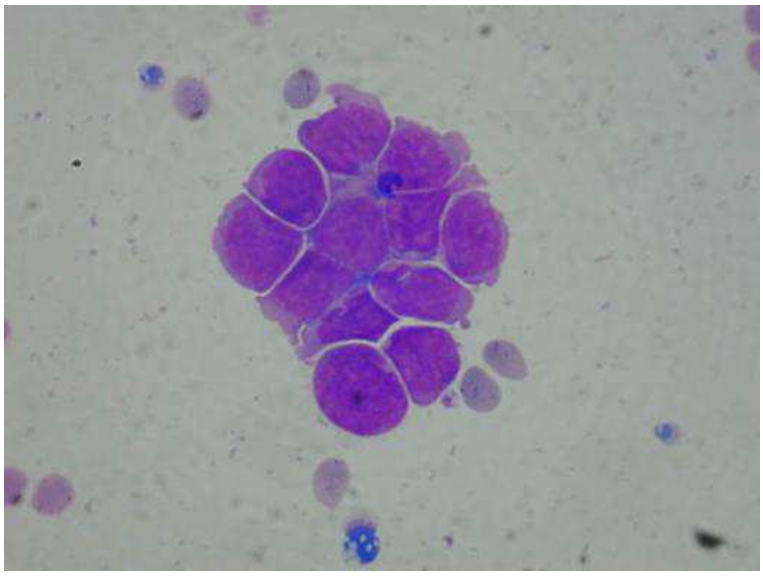
Initially enucleated children with pathology risk factors such as postlaminar optic nerve or choroidal invasion do not conclusively benefit from these procedures, but most authors perform them. In less advanced cases such as those in whom eye-conservative therapy is considered, these studies have a low yield. It is important to be able to conclusively identify malignant cells in these evaluations by using immunocytological and immunohistochemical tests since false positive examinations may falsely upstage the patients and cause overtreatment leading to potentially severe sequelae. The use of immunocytology for GD2 has been reported effective for this indication.[3, 5] When not available, identification of non-hematopoietic cells by flow cytometry by their lack of expression of CD45 is a useful, widely available confirmatory test.

C. Figure 5
Bone marrow aspirate showing metastasis of retinoblastoma (May-Grunwald-Giemsa staining; magnification, ×100).



The CSF should be examined only in high-risk patients. It is important to note that if the cell count is normal, the cells may adhere to the test tube and may therefore be undetectable. In all cases, examination of the cytocentrifugate should be performed, along with immunocytological analysis if possible, to improve the diagnostic accuracy of these procedures.

C. Figure 6
CSF containing retinoblastoma cells (May-Grunwald-Giemsa; magnification, ×100).



C.3 *Diagnosis and Evaluation of the Extent of Disease*

Mandatory tests

- Ocular examination by an experienced ophthalmologist, under anesthesia
- B-scan ultrasonography of the eye CT/MRI of the CNS and orbit, with and without contrast enhancement

Tests for advanced disease (stage 2 or higher)

- Analysis of bone marrow aspirate and biopsy specimens (from at least 4 sites)
- Analysis of the CSF obtained by lumbar puncture, followed by microscopic examination of the cytospin
  Bone scintigraphy (only for symptomatic patients or those with stage 4 disease)
- Abdominal ultrasonography (only for patients with stage 4 disease)

More Oncopedia resources about secondary leukemia:

- Secondary Acute Myeloblastic Leukemia in a Child with Retinoblastoma who was Treated with Chemoreduction

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C. References

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D. Staging and Grouping Retinoblastomas

There are 2 different aspects to the grouping and staging of retinoblastomas. The first aspect is related to disease extension in the eye, and this aspect is important for predicting eye preservation. The second aspect is related to assessing extraocular extension in order to predict patient survival.

The Reese-Ellsworth grouping for intraocular retinoblastomas was developed in the 1960s to predict the characteristics of eyes that had a greater chance of preservation after external beam radiotherapy.[1] Since this treatment modality is nowadays not recommended as an up-front alternative, a new grouping system was developed with the goal of classifying intraocular disease on the basis of the results of modern treatment modalities such as chemoreduction.[2,3] However, the Reese-Ellsworth system remains the gold standard against which newer systems should be tested.

It is important to consider that this grouping system has been subject to modifications by different groups, so when analyzing results, these modifications should be considered. The staging system for extraocular disease is even more controversial.

There are at least 5 staging systems that aim to evaluate patient survival.[4] Therefore, it is impossible to compare treatment results among groups. A consensus staging system was published in 2006. This new staging system has been further discussed by investigators from centers in South and North America, Europe, and South Africa and has been consolidated into a consensus document that includes the details of specimen processing after enucleation.[5,6] This proposed staging system is aimed to categorize patients according to risk of death from retinoblastoma and is not related to ocular survival. For this staging system to be successful, i.e., to achieve reliable and comparable results, it is critical to precisely define the invasion of ocular coats and outline the processing of enucleated eyes.[6] More recently, the TNM staging system was also updated and it is used by different groups worldwide.

D.1 *The Reese-Ellsworth Grouping System*[1]

Group I: Very favorable for maintenance of sight
- A. Solitary tumor, smaller than 4 disc diameters in size, at or behind the equator
- B. Multiple tumors, none larger than 4 disc diameters in size, all at or behind the equator

Group II: Favorable for maintenance of sight
- A. Solitary tumor, 4–10 disc diameters in size, at or behind the equator
- B. Multiple tumors, 4–10 disc diameters in size, behind the equator

Group III: Possible for maintenance of sight
- A. Any lesion anterior to the equator
- B. Solitary tumor, larger than 10 disc diameters in size, behind the equator

Group IV: Unfavorable for maintenance of sight

A. Multiple tumors, some larger than 10 disc diameters in size
B. Any lesion extending anteriorly to the ora serrata

Group V: Very unfavorable for maintenance of sight

A. Massive tumors involving more than one half of the retina
B. Vitreous seeding

D.2 *International Classification of Intraocular Retinoblastomas* [2]

Group A
Small tumors away from the foveola and optic disc

- Tumors with greatest dimension <3 mm confined to the retina, and
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

Group B
All remaining tumors confined to the retina

- All other tumors confined to the retina not in Group A
- Subretinal fluid (without subretinal seeding) <3 mm from the base of the tumor

Group C
Local subretinal fluid or seeding

- Local subretinal fluid alone >3 to <6 mm from the tumor
- Vitreous seeding or subretinal seeding <3 mm from the tumor

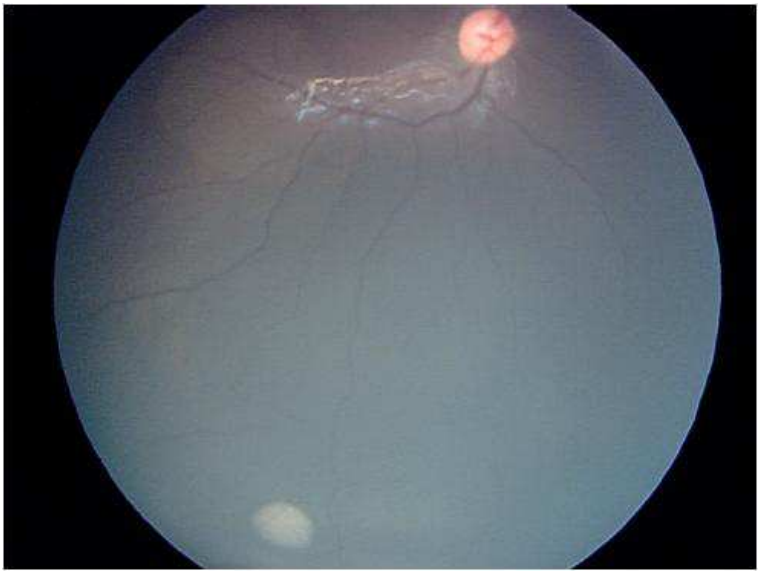
Group D
Diffuse subretinal fluid or seeding

- Subretinal fluid alone >6 mm from the tumor
- Vitreous seeding or subretinal seeding >3 mm from the tumor

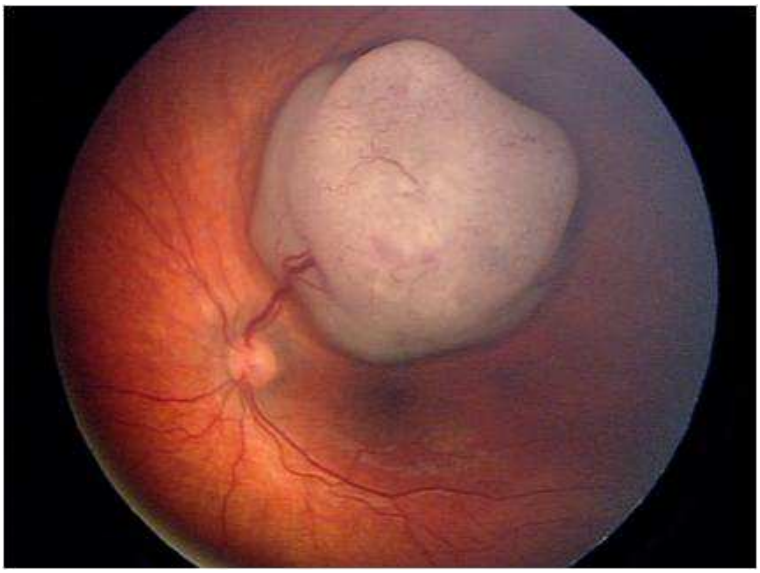
Group E
Presence of any or more of these poor prognostic features

- Tumor occupies more than two-thirds of the globe *
- Tumor in the anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media due to hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

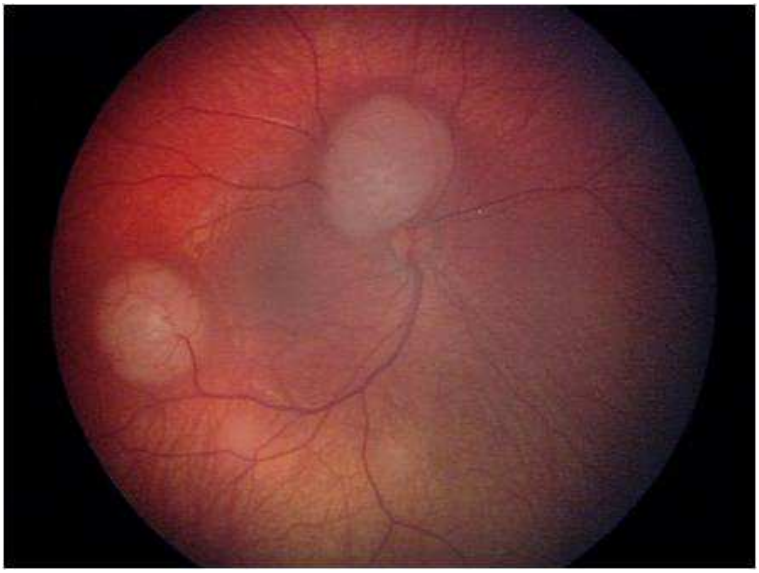
D. Figure 1
Group A: Small tumor (≤3 mm) confined to the retina at a distance from the foveola and optic nerve.



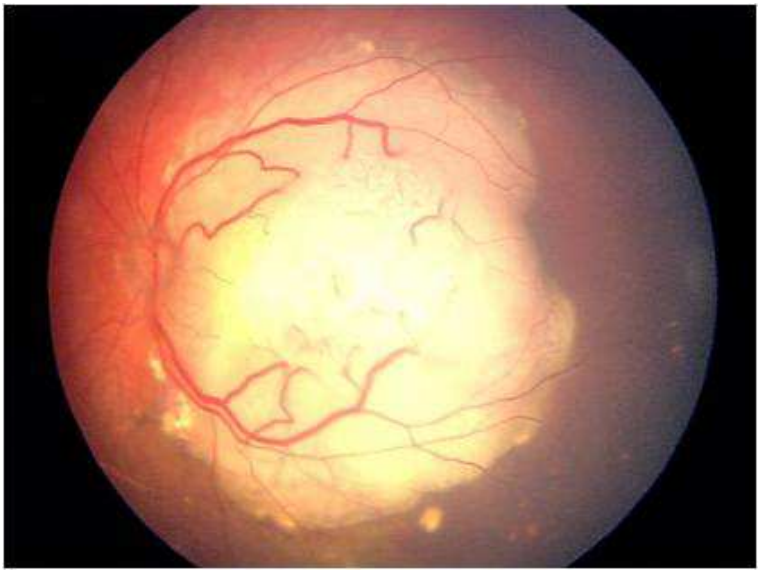
D. Figure 2
Group B. Tumors >3 mm, confined to the retina



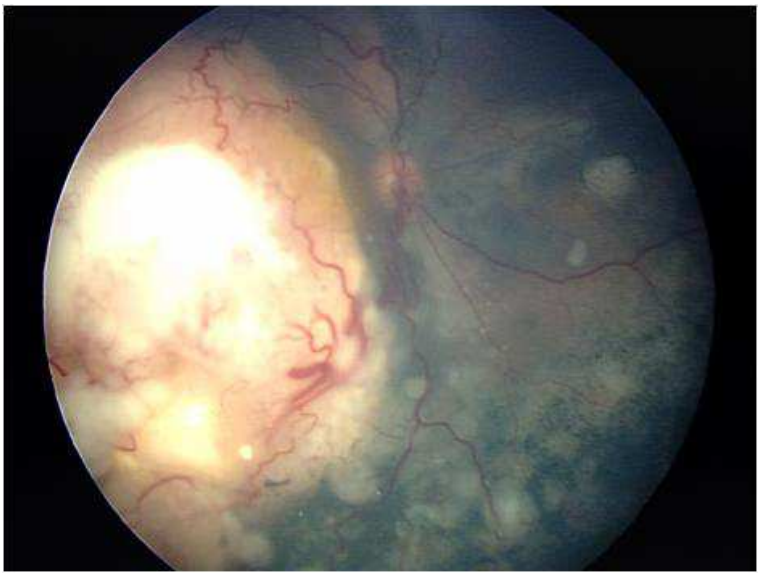
D. Figure 3
Group B: Small tumors (≤ 3mm), confined to the retina, but in close proximity to optic nerve and foveola.



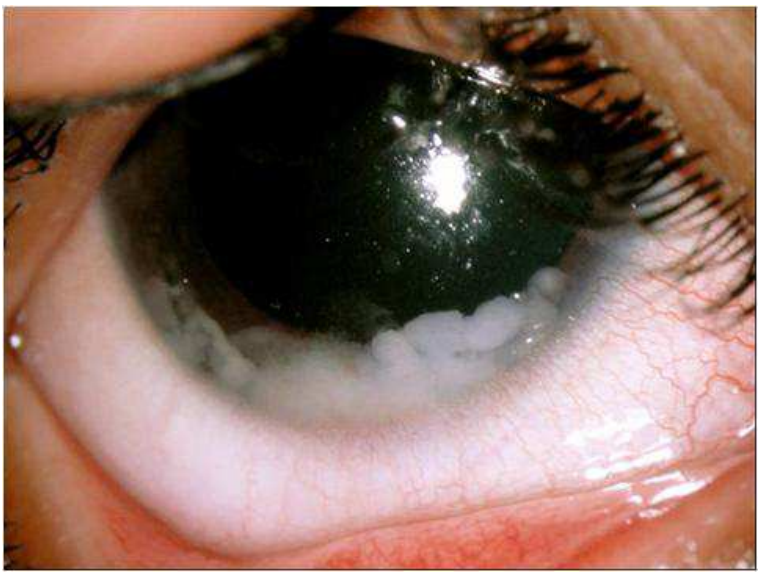
D. Figure 4
Group C. Tumor with localized subretinal fluid and local seeding.



D. Figure 5
Group D. Tumor with diffuse seeding



D. Figure 6
Group E. Tumor in the anterior segment



D. 3 *International Retinoblastoma Staging System.* [5]

Stage 0: Patients (eyes) treated conservatively
Stage 1: Eyes enucleated with completely resected tumors
Stage 2: Incompletely resected/completely resected tumor with microscopic residual disease
Stage 3: Regional extension
    a. Overt orbital disease
    b. Preauricular or cervical lymph node extension

Stage 4: Metastatic disease
1. Hematogenous metastasis
    1. Single lesion
    2. Multiple lesions
2. CNS extension
    1. Prechiasmatic lesion
    2. CNS mass
    3. Leptomeningeal and CSF disease

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[6]Sastre X, Chantada GL, Doz F, et al. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. *Arch Pathol Lab Med.* 2009;133(8):1199-202.

E. Treatment of Retinoblastoma

Treatment of retinoblastoma involves 2 different scenarios: (i) eye-preserving treatment, when intraocular disease allows for a conservative approach (i.e., to save the patient's vision), and (ii) life-saving treatment, when eye conservation is not possible, and treatment is aimed at saving the patient's life.

E.1 *Enucleation*

Enucleation is the simplest and safest therapy for retinoblastoma[1] During this procedure, an orbital implant is usually fitted and attached to the extraocular muscles. In the past, orbital implants were previously avoided because they were thought to interfere with the palpation of the socket and the clinical detection of orbital recurrence. However, thanks to the improved understanding of associated histologic risk factors and the availability of better imaging techniques to detect orbital disease, implants should be placed at the time of enucleation. This procedure demands resection of the long stump of the optic nerve. Enucleation performed within the first 2 years of life leads to the development of facial asymmetry because of the inhibition of orbital growth. Enucleation of a child with a suspected retinoblastoma should be performed by an experienced pediatric ophthalmologist.

What are the Indications for Enucleation as the Initial Treatment for Retinoblastoma?

- Secondary glaucoma
- Invasion of the anterior segment (anterior chamber and iris)
- Rubeosis iridis
- Cases where follow-up is impossible or local therapy poses limitations
- Eyes classified as Reese-Ellsworth (R-E) group Vb, with unilateral and nonhereditary disease

What are the Contraindications for Enucleation as the Initial Treatment for Retinoblastoma?

- Massive extraocular dissemination
- Cases of less-advanced intraocular disease and when local therapy and adequate follow-up is possible
- Buphthalmia with no evidence of overt extraocular dissemination[2]

When is Orbital Exenteration Indicated?

Orbital exenteration is almost never indicated. It should not be attempted as an initial procedure in cases of retinoblastoma with orbital extension since retinoblastoma is sensitive to chemo- and radiotherapy. Preoperative chemotherapy (2–4 cycles) or radiotherapy usually shrinks the tumor sufficiently to allow secondary enucleation.

What are the Indications for Secondary Enucleation?

- Lack of tumor control after local therapy
- Cases of extraocular disease treated with neoadjuvant chemotherapy

Which Surgical Procedures should be Avoided in Cases of Retinoblastoma?

- Pars plana vitrectomy
- Enucleation taking a short stump of the optic nerve
- Anterior chamber paracentesis
- Orbital exenteration in cases of extraocular disease

E.2 *Focal therapy*

Focal treatments, are used for small tumors (<3–6 mm) usually in patients with bilateral disease, and in combination with chemotherapy. *Photocoagulation* with argon laser therapy is used to treat tumors situated at or posterior to the equator and tofor the treatment of retinal neovascularization due to radiation therapy.[2]

The treatment is aimed at delimiting the tumor and coagulating all blood supplied to the tumor, and 2 or 3 monthly sessions are usually required.

Cryotherapy is used for the treatment of small equatorial and peripheral lesions.[3] The treatment involves 1 or 2 monthly sessions of triple freeze and thaw cycles. Tumor control rates are usually excellent with this treatment. *Transpupillary thermotherapy* involves the application of focused heat at subphotocoagulation levels, usually with a diode laser. In thermotherapy, the goal is to deliver a temperature of 42–60°C to the tumor for 5–20 minutes, while sparing retinal vessels from photocoagulation.[4]

E.3 *Radiotherapy*

Radiotherapy in combination with focal treatments can provide excellent tumor control because retinoblastoma is a very radiosensitive tumor.[5] However, since radiation therapy increases the risk of secondary malignancies in retinoblastoma survivors,[6] contemporary management of intraocular retinoblastoma is designed to avoid or delay its use. Radiotherapy is mainly as salvage method for eyes that have failed to respond to chemotherapy and focal treatments, usually because of the progression of vitreous and subretinal seeding. Radiation therapy continues to play a major role in the treatment of patients with extraocular disease.

Since most patients with intraocular retinoblastoma undergoing radiotherapy have multifocal disease, the entire retinal surface needs to receive a uniform dose of radiation. The therapy can be administered using several techniques, usually through lateral or anterior fields. The recommended total dose is 4,000–4,500 cGy, administered in 180–200 fractions. However, the feasibility of doses of 3,600 cGy in conjunction with other techniques is being investigated.[5,7]

Radioactive plaque therapy is useful for treating localized tumors, both because it requires a short procedure time and because it delivers a high dose of irradiation to the areas of interest, while minimizing the effects of radiation onextraocular structures.[8] Plaque therapy is indicated for solitary tumors with a diameter ranging between 6–15 mm, tumors with a thickness of ≤10 mm, and lesions located more than 3 mm away from the optic disc or fovea. The radioactive implant is placed on the sclera over the base of the tumor and is kept for 2–4 days, which is the time needed to deliver approximately 4,000 cGy to the apex of the tumor. Different episcleral radioactive plaques can be used, although 125I is the most widely used radionuclide. Control rates of 85–90% can be achieved with this method.[8]

E.4 *Chemotherapy*

Chemotherapy was previously used only to treat metastatic disease; however, since the mid-90s, it has been widely used as the primary treatment for intraocular disease not amenable to local therapy. Systemic chemotherapy is used to decrease the tumor size and make the tumors suitable for local therapy.[9-12] This approach, called chemoreduction, aims to prevent enucleation or the use of external beam radiotherapy (EBRT) in selected cases. Carboplatin is the most frequently used chemotherapeutic agent since it penetrates the eye well and is highly effective in retinoblastoma cases, as revealed by phase II studies.[13,14] Vincristine and etoposide are also used; however, their ability to penetrate into the eye is lower.[14] Animal studies suggest that the combination of carboplatin and topotecan has high penetration to the vitreous.[15] However, this combination is too myelotoxic to be used for conservative therapy when both drugs are used intravenously, but topotecan combined with vincristine proved to be an effective combination with manageable toxicity.[16]

Most intraocular tumors shrink dramatically after systemic chemotherapy; however, consolidation with local treatment is needed in most cases, to prevent relapse.[17,18] The response to chemotherapy depends on the tumor location, patient age, and tumor size.[12,19,20] Using these techniques, the salvage rates for eyes of groups A-B approaches 100%, and most patients avoid both enucleation and EBRT.[19] Children with group C eyes have also a favorable outcome with this treatment. For patients with advanced intraocular tumors, especially those with vitreous seeding the ocular salvage rates are usually in the range of 30% and EBRT is usually required.[7,21]

A major proportion of failed treatments are attributed to extension of the tumor into the vitreous or the subretinal region, where antineoplastic agents do not easily penetrate. Carboplatin diffuses well into the vitreous, its intraocular concentrations are 7–10 times higher when it is administered subconjunctivally, and animal studies have shown that this route of administration results in a dose-dependent inhibition of intraocular tumor growth. Despite these encouraging preclinical data, there has been no tangible improvement in the outcome of eyes with advanced disease.[22] Topotecan is another drug that was evaluated for its periocular use.[23] However, despite its favorable pharmacokinetics, the results in terms of preservation of affected eyes are poor.[24] The Children's Oncology Group (COG) performed a prospective study to evaluate the effectiveness of this modality of carboplatin administration[25] but the results of this study are not available at the time of writing this chapter. Thus periocular chemotherapy has been abandoned by most groups for the treatment of retinoblastoma.

The treatment of patients with advanced intraocular disease (R-E groups IV and V, international groups C and D) remains a major challenge. Although randomized studies have not been performed, compared to radiation and focal treatments alone, chemoreduction with systemic chemotherapy does not seem to significantly improve the overall ocular salvage rate in patients with advanced intraocular disease.[26]

Tumors in the central retina usually respond better to chemotherapy than tumors in the peripheral retina. However, large central tumors may show subretinal seeding, which ultimately may lead to treatment failure. Despite the addition of aggressive strategies for sequential focal therapy, the rate of global drug retention remains at ≤50% for eyes of R-E group V (group D), and most patients eventually require radiotherapy. EBRT used as consolidation therapy in these cases appears to yield better results in terms of eye preservation.[7] A major proportion of treatment failures are attributed to tumor progression into the vitreous or subretinal implants, 2 areas that antineoplastic agents do not easily penetrate. There are several strategies to improve the drug penetration to the vitreous. Carboplatin diffuses well into the vitreous, unlike etoposide.[27] The intraocular penetration of carboplatin is enhanced when the tumor disrupts the blood-vitreous barrier, and it is enhanced after cryotherapy.[28] Topotecan also shows good passage to the vitreous and it is being investigated as an alternative therapeutic agent for retinoblastoma.[15,28]

However, systemically administered chemotherapy fails to attain significant levels in the vitreous without causing unacceptable hematopoietic toxicity. Increasing systemic dose-intensity of chemotherapy is hence not recommended to increase the salvage rates of eyes affected with retinoblastoma. Innovative treatment modalities aiming to improve the drug concentration into the eyes without increasing systemic exposure have recently been developed. The most striking results were obtained with intra-arterial chemotherapy. These include the administration of chemotherapy through the ophthalmic artery via superselective catheterization,[29,30] a technique that Japanese investigators pioneered to treat eyes with advanced disease in patients whose families decided against enucleation.[31] This group pioneered the administration of melphalan, based on their in vitro cytotoxicity studies. In the mid-2000s, the New York group refined their strategy and implemented a superselective catheterization of the ophthalmic artery in order to deliver higher doses of chemotherapy to the eye.

This treatment, including single agent melphalan was initially administered to children with unilateral retinoblastoma with advanced intraocular disease with outstanding results and minimal toxicity.[30] Based on these encouraging results, the same group administered other agents such as carboplatin and topotecan to other patients with bilateral disease and relapsed-resistant eyes with excellent results.[32] These outstanding results encouraged other centers to adopt this strategy with overall excellent results.[24,33] However, intra-arterial chemotherapy proved to be a highly specialized treatment and some complications limited to the eye were noted by some groups in their early experience. Foreign body material caused by cotton embolization was found in enucleated eyes in one report,[34] III cranial nerve palsies were found in a significant number of patients from another group[35] and animal models and clinical data suggested vascular damage mainly to the choroid,[36,37] rising concern about the potential late effects of this treatment. Other authors expressed their concern in the radiation dose that the patients undergoing receive which for patients with the germline mutation of the Rb1 gene could be excessive if not carefully monitored.[38]

As the use of intra-arterial chemotherapy became more widespread, most centers applied other drugs besides melphalan. Melphalan is an active drug against retinoblastoma, but as an alkylating agent, its use in children with germline mutations of the Rb1 gene should be limited. Despite low concentrations of the drug are expected in the bloodstream after intra-arterial chemotherapy, melphalan is detected in children receiving this treatment potentially causing late effects.[39] In addition, melphalan seems to penetrate less to the vitreous compared to topotecan.[39] Even though a cause-effect link between the above-mentioned toxicity and melphalan is not yet clear, many authors consider that other drugs such as carboplatin or topotecan may be less toxic to the eye when give intra-arterially and most groups now use the three drugs which may be more effective for eyes with recurrent disease.

Many questions about doses, schedule and indications still persist, and unfortunately no prospective comparative study was performed.[67] Intra-arterial chemotherapy is seldom feasible in smaller children,[68] so some authors administered it after a course of systemic chemotherapy.

In the light of the knowledge available at the moment of writing this chapter, intra-arterial chemotherapy, though increasingly used by most of the leading retinoblastoma centers worldwide, is a very sophisticated therapy only available in selected institutions, needing meticulous care to many details, so its generalization is still a challenge. Most centers are using it for the treatment of relapsed intraocular retinoblastoma and some are now using it for frontline treatment of group D disease in bilateral cases. In children with unilateral disease and group D disease, there is a vivid controversy about its use. In these children, encouraging results in eye preservation were reported but often with poor vision.[32] Other groups consider that these children with unilateral disease and group D tumors in whom little vision would be achieved should be enucleated upfront, because they consider that micrometastatic disease may be missed and these children may have a poorer survival.[32] However, there is no conclusive data supporting each strategy. As a concept, in settings where a higher proportion of patients present with pathology risk factors, enucleation should be a safer approach, but in centers where this presentation is less common, there should be no significant difference in survival.

Other researchers developed devices for improving the transscleral passage of chemotherapeutic agents through the periocular[43-45] or intravitreous administration of chemotherapy [46,47] or gene therapy.[48] Intravitreous chemotherapy became more popular in the past few years. Despite being contra-indicated for many years because a concern of possible orbital seeding during the procedure, intravitreal injection of chemotherapy is now a well-established therapy, especially for eyes with vitreous seeds.[49] A careful technique for its application is needed to avoid orbital seeding.[50]

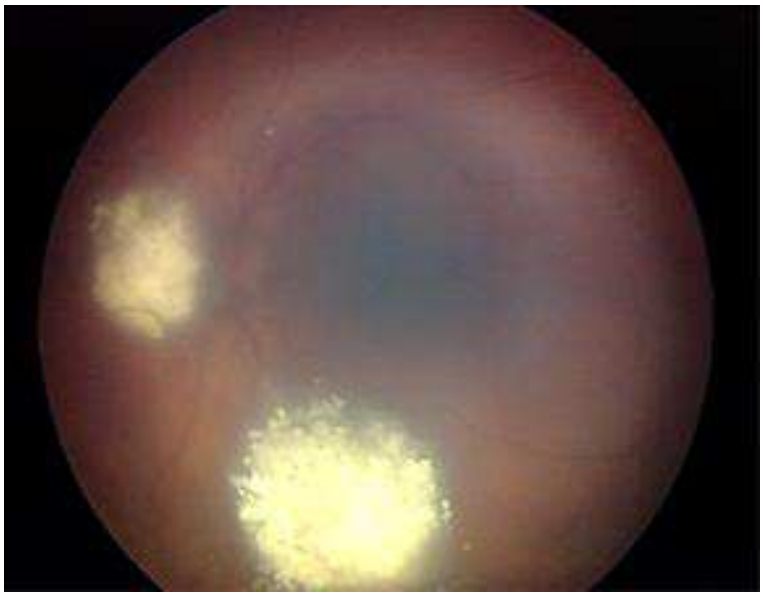
Melphalan is the most commonly used drug, but topotecan has also been explored in animal studies. It is important to know that intra-vitreal chemotherapy and intra-arterial chemotherapy have their own different indications and no-one is a substitute for the other. Conceptually, eyes that benefit the most with intra-arterial chemotherapy such as those with retinal detachment are not suitable candidates for intravitreal chemotherapy whereas those with massive vitreous seeding remaining after therapy may benefit most with intra-vitreal chemotherapy. However, the results of the use of these techniques are still being evaluated.

One major advantage of the use of local chemotherapy would to avoid or reduce the leukemogenic effect of systemic chemotherapy. Some of the concerns pertain to the long-term results and safety of current strategies since some drugs, especially epipodophyllotoxins, are known to induce secondary leukemia.[51] Therefore, the composition of chemotherapy regimens, as well as the duration of treatment, is still debated. Even though the incidence of secondary leukemia appears to be low, it is an almost uniformly fatal complication occurring in children whose risk of death because of their malignancy is negligible.

As a conclusion, the final word about conservative therapy for retinoblastoma has not been said. Since tumor control is heavily dependent on local therapy, which in turn is critically influenced by the expertise of the attending physicians, a methodological bias exists for determining the efficacy of a chemotherapy regimen. The status of the contralateral eye is also an important factor to consider when selecting a treatment modality because it may influence the eye-preservation rate. Finally, this treatment is tedious and requires meticulous management and technical support, which is only available in specialized centers.

E. Figure 1
Chemoreduction in retinoblastoma
A: Before chemotherapy

B: After 2 cycles of therapy with vincristine and carboplatin



E.5 *Status of Conservative Therapy in Developing Countries*

Although systemic chemoreduction regimens have been successfully applied in developing countries, their use is limited by factors like the lack of availability of sophisticated therapies, uncertainty of follow-up for high-risk patients, advanced disease, lack of trained personnel, and insufficient staffing.[5,6] In less developed countries, chemoreduction and local therapy are feasible as conservative treatments only if patient compliance is optimal. There have been reports of deaths due to toxicity or in cases where patients decide against enucleation.[52-54] In developing countries, all these factors should be considered before initiating a chemoreduction program. The fact that enucleation is curative in most cases of intraocular retinoblastoma should be recognized, because treatments for preserving the function of eyes with advanced disease may result in extraocular dissemination, which is seldom curable. However, a recent study on patients from Brazil and Argentina showed that chemoreduction did not increase the risk of extraocular relapse.[7] This treatment should be carried out in centers with adequate facilities and excellent patient compliance. Intra-arterial chemotherapy is used in some middle income countries, but it is certainly not a priority in centers from lower income countries.

E.6 *Adjuvant Chemotherapy for Retinoblastoma*

Some histopathological features are considered to be risk factors for extraocular relapse after enucleation. These include invasion of the choroid, sclera, optic nerve, and the anterior segment. The role of adjuvant chemotherapy in reducing the rate of relapse for patients with putative histopathological risk factors for relapse is a matter of controversy.[8,9,55] Careful postenucleation histopathological staging is essential to determine the risk of relapse.

In developing countries, adjuvant therapy cannot be appropriately customized because facilities for reliable pathological examination of enucleated eyes are lacking. In some cases, pathological examination is not even performed on enucleated eyes.[56]

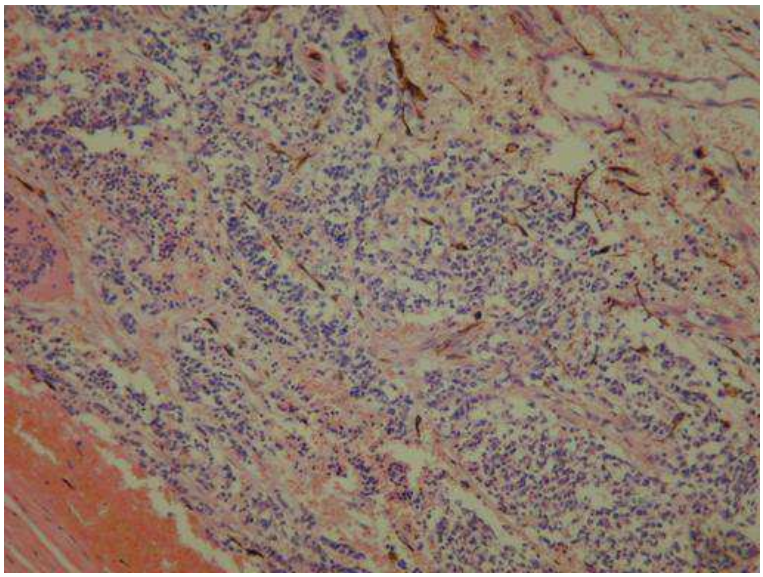
Many centers have widely varying definitions of the degree of invasion into the ocular coats. The International Retinoblastoma Staging Working Group recently published a guideline for eye processing, intended to be disseminated in developing countries. This guideline provides consensus-based definitions for the different degrees of invasion into the ocular coats.[57] In developing countries, pediatric oncologists are faced with the dilemma of prescribing adjuvant chemotherapy to all patients with putative risk factors, avoiding it in controversial cases, and aggressively treating patients with relapse. Adjuvant chemotherapy does not completely eliminate the possibility of extraocular relapse, and its advantages are not proven in groups with low relapse rates.

Because of the low relapse rate among most patients in these populations, a randomized study comparing adjuvant treatment with observation would require a very large number of patients. Many authors consider extraocular relapse to be a catastrophic event and recommend adjuvant therapy for all patients with histopathological risk factors.[36] However, in recent years some groups shown that intensive therapy can salvage eyes in many patients with relapse.[9,10] Therefore, avoiding administering adjuvant chemotherapy to patients with a low relapse rate and aggressively treating those with relapse is a reasonable alternative.

There is an almost universal consensus that adjuvant chemotherapy is not needed for patients with intraretinal disease or prelaminar optic nerve invasion. The role of chemotherapy in cases of isolated choroidal invasion remains controversial. It has been suggested that once the tumor cells have invaded the choroid, they may enter systemic circulation, giving rise to hematogenous metastasis.

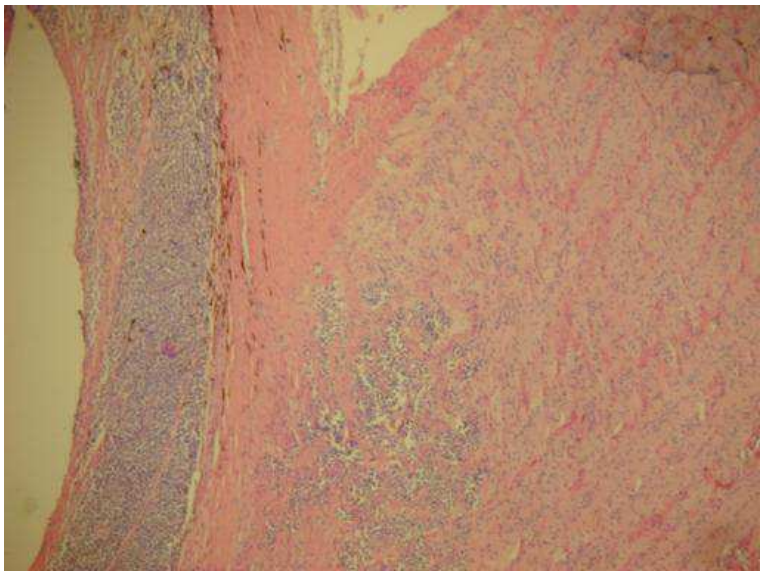
Children with massive choroidal invasion, as defined by the IRSS have about a 5% risk of extraocular relapse if no adjuvant therapy is give.[58] The relapse risk of children with focal choroidal invasion is about 1%. Despite this difference is significant, since some relapsing patients may be rescued with intensive therapy, there was no difference in overall survival of these children.[58] Patients with choroidal invasion combined with postlaminar optic nerve invasion are at higher risk of relapse and should receive adjuvant chemotherapy.[11]

E. Figure 2
Choroidal invasion



Invasion of the optic nerve beyond the lamina cribrosa is a major risk factor for relapse, especially when the cut end is involved.[9,12]

E. Figure 3
Postlaminar optic nerve extension



When the cut end is tumor-free, the optimum management is controversial, but most groups recommend adjuvant chemotherapy.[59] Some patients seem to be at a higher risk for relapse, such as those with extensive major invasion of the choroid, with or without scleral invasion.[37] One series showed that higher-dose chemotherapy yielded better results in these patients than in historical controls.[60] A recent multicentric study from France showed excellent results with the use of a lower intensity regimen, albeit in a small population of higher risk children.[61] Orbital radiotherapy is not necessary for these patients. There have been only a few reports in the literature on patients receiving neoadjuvant chemotherapy for postlaminar optic nerve invasion, as evidenced by imaging.[62,64] However, identifying postlaminar optic nerve invasion through imaging studies is a challenge.[63] Although this modality may reduce the number of cases of tumor development at the resection margin of the optic nerve, but a combined ophthalmological-neurosurgical approach may be necessary to obtain a long optic nerve stump.[64] The use of pre-enucleation chemotherapy has been advocated as a way of reducing the incidence of this complication.

A group in China reported an increased mortality in patients receiving pre-enucleation chemotherapy.[65] The authors postulated that the use of pre-enucleation chemotherapy masked pathology risk factors leading to undertreatment. However in their series, all relapsing children received inadequate adjuvant therapy with the available pathology and enucleation was performed after progressive disease in families not accepting enucleation. [66] In the setting of a prospective multicentric study, Luna Fineman et al reported that the use of pre-enucleation chemotherapy improved the survival results and decreased treatment abandonment in Central America.[67] Hence, especially in developing countries, pre-enucleation chemotherapy may be recommended when families do not accept initial enucleation or in those with severe buphthalmia. However, enucleation should never be withheld and it should be done within 2 or 3 cycles. Because the pathology of these eyes may not be accurate to identify risk factors, these children should receive adjuvant therapy in all cases.[68]

Patients with tumor invasion of the cut end of the optic nerve are uniformly considered to be at a high risk for relapse.[59,69] The reported survival rate is as low as 40%,[69] and these patients require adjuvant chemotherapy and orbital radiotherapy for adequate treatment.[70,71] The effectiveness of intrathecal chemotherapy in such cases remains to be established. According to our limited experience, patients with microscopic scleral involvement are at a high risk for extraocular relapse and should receive adjuvant higher-dose chemotherapy. However, very few patients present with isolated scleral involvement; most have combined postlaminar optic nerve involvement, which makes it difficult to estimate the significance of scleral invasion as a risk factor.[72] Orbital radiotherapy does not seem to be necessary for these patients if intensive chemotherapy is administered.[72]

E.7 *Adjuvant Therapy in Retinoblastoma*

There is a general agreement that patients with the following features do not need adjuvant therapy:

1. Intraretinal invasion
2. Prelaminar optic nerve invasion
3. Focal choroidal invasion

There is also a general agreement that patients with the following features need adjuvant therapy:

1. Invasion of the resection margin of the optic nerve
2. Scleral invasion
3. Postlaminar optic nerve extension with tumor-free resection margins

A consensus has not been achieved for the following controversial subgroups:

1. Massive choroidal invasion
2. Anterior segment invasion

E.8 *Central Nervous System Disease*

Intracranial dissemination occurs by direct tumor extension through the optic nerve, and its prognosis is dismal.[73,74] Treatment for patients with this condition should include platinum-based intensive systemic chemotherapy and central nervous system (CNS)-directed therapy. Although intrathecal methotrexate (with or without cytarabine) has been traditionally used, there are no preclinical or clinical data to support its use. Other intrathecal agents with documented effects against retinoblastoma include topotecan and thiotepa. However, there is no evidence of their effects on patient outcome. Although the use of radiotherapy for patients with intracranial dissemination is controversial, responses have been observed with craniospinal irradiation using a dose of 25–35 Gy to the CNS and the spinal axis, with a booster dose (10 Gy) to sites of measurable disease.[75] Therapy intensification with higher-dose chemotherapy and autologous stem cell rescue has been explored, but its effectiveness remains unclear. Even with this treatment, very few patients survive.[76]

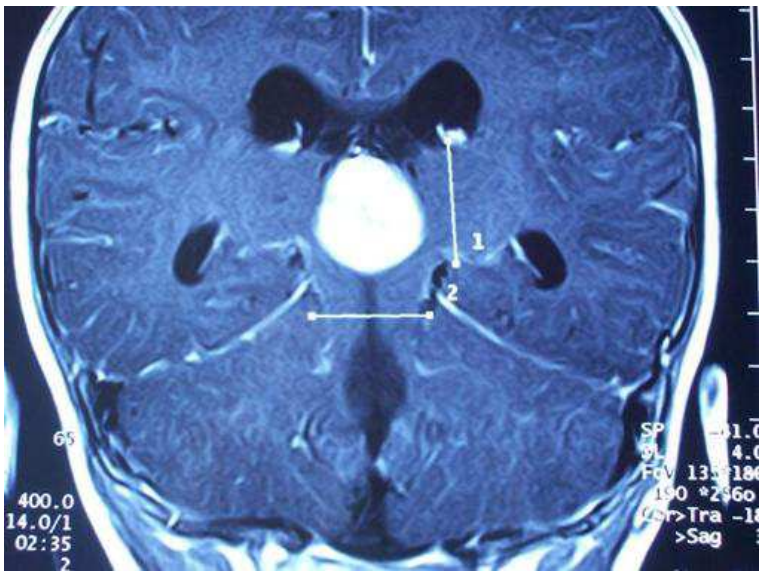
Despite the intensity of the treatment administered and the documented responses in cases of intracranial disease, patients usually succumb to the disease, and survivors are anecdotal.

E.9 *Trilateral Retinoblastoma*

The prognosis of patients with trilateral retinoblastoma is dismal; patients usually die of disseminated neuraxis disease in less than 9 months.[77] The incidence of trilateral disease appears to be affected by different factors such as geographic distribution and treatment received.[78,79] The rare survivors are usually those diagnosed through screening imaging and treated with intensive chemotherapy, with or without craniospinal radiation. Pineoblastoma occurring in patients without retinoblastoma is also associated with a poor prognosis. However, these patients can be cured with an appropriate aggressive multimodal approach.[80] Pineoblastoma is a chemosensitive neoplasm that appears to have a steep dose-response curve for alkylating agents.

Studies of older patients with primary pineoblastoma have recently shown that complete resection and intensive alkylator- and cisplatin-based therapy, followed by craniospinal irradiation (36 Gy with a 59-Gy booster dose to the pineal gland), and consolidation with high-dose chemotherapy and autologous stem-cell rescue, may improve the survival rates in more than two-thirds of all patients. It is therefore possible that similar treatment guidelines could be used for trilateral retinoblastoma. However, the serious long-term toxicity such high doses of radiation can produce in very young children should be considered. Therefore, current strategies are directed toward avoiding irradiation by using intensive chemotherapy followed by consolidation with autologous stem-cell rescue, an approach similar to those adopted for treating brain tumors in infants.

E. Figure 4
Trilateral retinoblastoma (MRI)



E. Figure 5
Trilateral retinoblastoma (MRI)

Because of the poor prognosis of patients with trilateral retinoblastoma, screening neuroimaging for this condition is a common practice. One-fourth of the cases in the literature were identified during screening. Given the short interval between the diagnosis of retinoblastoma and the development of trilateral retinoblastoma, routine screening could help in detecting most cases within 2 years of the onset of the disease. While it is not clear whether early diagnosis can affect survival, performing neuroimaging every 6 months until patients reach the age of 5 years is usually recommended.

E.10 *Extracranial Metastatic Retinoblastoma*

Hematogenous metastases occur in the bones; bone marrow; and, less frequently, the liver. Although conventional chemotherapy may improve the long-term survival rate, these cures should be considered anecdotal. Metastatic retinoblastoma is not curable with conventional chemotherapy. In recent years, however, small series have shown that metastatic retinoblastoma can be cured using high-dose chemotherapy and autologous stem-cell rescue.[81-84] This approach is similar to that adopted for metastatic neuroblastoma and involves short and intensive induction regimens, which usually contain alkylating agents, anthracyclines, etoposide, and platinum compounds, followed by consolidation with autologous hematopoietic stem-cell transplantation. Using this approach, the outcome appears to be encouraging. If megatherapy consolidation is used, the agents should be carefully selected.

In general, recurrence are generally intracranial, and for this reason, agents with proven efficacy in intracranial retinoblastoma should be used. In this regard, the combination of carboplatin and etoposide has been shown to be effective against CNS disease and should be part of the regimen.

In the largest published series, 7 patients received consolidation therapy with the CARBOPEC combination (carboplatin, 1,250–1,750 mg/m2; etoposide, 1,750 mg/m2; and cyclophosphamide, 6.4 g/m2); treatment was successful in 5 cases and failed in 2 cases, with the patients developing CNS relapse.[82] Other groups have used a thiotepa-based consolidation regimen (thiotepa, 900 mg/m2; etoposide, 750–1,200 mg/m2; and carboplatin, 1,500 mg/m2).[81] There is a strong rationale for using thiotepa.

Retinoblastoma is responsive to alkylating agents such as thiotepa, a group of agents for which dose escalation is shown to overcome resistance. Furthermore, thiotepa has excellent CNS-penetration ability. An interesting observation is that patients with distant bone metastases (outside the orbit and skull) who respond well to induction chemotherapy may not require radiation therapy when treated with autologous stem cell rescue.

E.11 *Orbital Retinoblastoma*

In most cases, disease disseminating to the orbit and/or the preauricular lymph nodes is curable with an aggressive approach involving neoadjuvant chemotherapy, enucleation, and adjuvant therapy with chemotherapy and radiationtherapy.[85] Orbital exenteration is no longer recommended for these patients, and chemotherapy should be the initial approach. Tumors usually shrink with this therapy, and therefore enucleation becomes possible after 2 or 3 cycles. In cases of overt extraocular disease, distant metastatic disease canshould be readily ruled out since patients with metastasis should receive a more intensive approach. Orbital relapse after enucleation is also curable with the same approach.

E.12 *Second Malignancies in Retinoblastoma Survivors*

Children with the germ-line mutations of the *RB1* gene are at increased risk of secondary non-retinoblastoma malignancies.[86] This factor is a key determinant in choosing the treatment for these patients . The germline Rb1 mutation predisposes these children to secondary malignancies later in life, but this risk is also influenced by treatment received.[6] The use, dose and possibly the age when radiation therapy was administered increases the risk of secondary tumors in the irradiated field.[87] The most frequent secondary malignancies are sarcomas with may occur in the irradiation field or elsewhere in the body, including soft tissue tumors or limb osteogenic sarcoma. The latter tend to occur in adolescence whereas the former usually occur later in life. Skin tumors such as melanoma and also epithelial tumors have been reported, so these patients should avoid excessive exposure to sunlight. Increased risk for epithelial cancers has also been reported. Survival from a second tumor is higher when early diagnosis is achieved, so some authors recommend specific surveillance to detect these tumors earlier. Mortality for secondary acute leukemia is, on the contrary high and only preventable by avoiding leukemogenic agents. Overall, the prevalence of secondary malignancies increases with age, leading to a mortality rate of 25% to 50 years of age,[88] although with modern therapies, it may be much less.[89] Patients with non-hereditary retinoblastoma are not at an increased risk of second malignancies compared to the general population.[88]

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